HEALTH & MEDICINE

The Troubled History of Cancer Risk Assessment

The Linear-No-Threshold paradigm, which asserts there are no safe exposure levels, is the product of flawed and corrupted science.

BY EDWARD J. CALABRESE

When crafting regulations on exposure to carcinogens and other dangers, policymakers often vow to "follow the science" on what is safe and what is unsafe. But what if that science is flawed or grounded in questionable judgments—or worse?

In 1956, a National Academy of Sciences (NAS) panel formally recommended to the U.S. Government that it change how it assesses risk from ionizing radiation. That sounds innocuous enough, but the Biological Effects of Atomic Radiation (BEAR) I Genetics Panel's proposed change was momentous: switching from a threshold model in which exposure is deemed safe if kept below a certain level, to a linear model in which no exposure is considered safe. This recommendation would ultimately be accepted by leading regulatory and advisory bodies in the United States and internationally, and extended to other prospective hazards like chemical carcinogens.

As the saying goes, "As the twig is bent, so grows the tree." All subsequent cancer risk assessments in the United States and throughout the world would inherit the risk assessment paradigm from the NAS BEAR I Genetics Panel. But was this change sound?

X-RAY MUTATIONS

The NAS BEAR I Genetics Panel based its recommendation mainly on a strongly held belief that all radiation-induced mutation was unrepairable, irreversible, cumulative, and linear in the matter of dose response. However, the empirical evidence for this view was weak and equivocal. Yet the recommendation had considerable authority because the panel was deemed by opinion leaders, including the *New York Times*, as a virtual genetics "dream team" that included a Nobel laureate, a future laureate, and others of high achievement and prestige.

The origin of the Linear-No-Threshold (LNT) belief was borne in the judgment and passion of Hermann Muller, who was the first to claim that X-rays induced gene mutations. Muller had indeed made a momentous breakthrough in late 1926 when he found a way to produce quickly copious transgenerational phenotypic changes (e.g., alterations in size, color, or shape) in fruit flies, which he interpreted as being the result of gene mutation. This was something that no one else had done. Muller believed that he had discovered the long-sought mechanism of evolution, as he claimed that he had produced the "artificial transmutation of the gene." He even introduced the term "point mutation" (i.e., very small mutational gene change) into the geneticist's lexicon.

Muller rushed to publish his discovery after only the first of the three seminal experiments that would ultimately earn him a Nobel Prize. However, the first article, published in the journal *Science*, offered no data, instead presenting a discussion of his observations. Several months later and with considerable suspense, he unveiled the data at a large conference in Berlin, to great acclaim. (The relevance of all this will be explained below.) His star rose meteorically and he became the clarion of "the new genetics" that gained insight into evolution as well as medical concerns resulting from excessive use of X-rays.

Just when the initial commotion settled down, Muller made headlines a second time, in 1930, when he announced that the nature of the dose response for X-ray-induced mutation was linear, all the way down to a single ionization. That is, he claimed, there is no safe exposure. He thought this idea was basic, a universal concept, occurring in all life, including the plant, microbe, and animal domains, and called it the "Proportionality Law."

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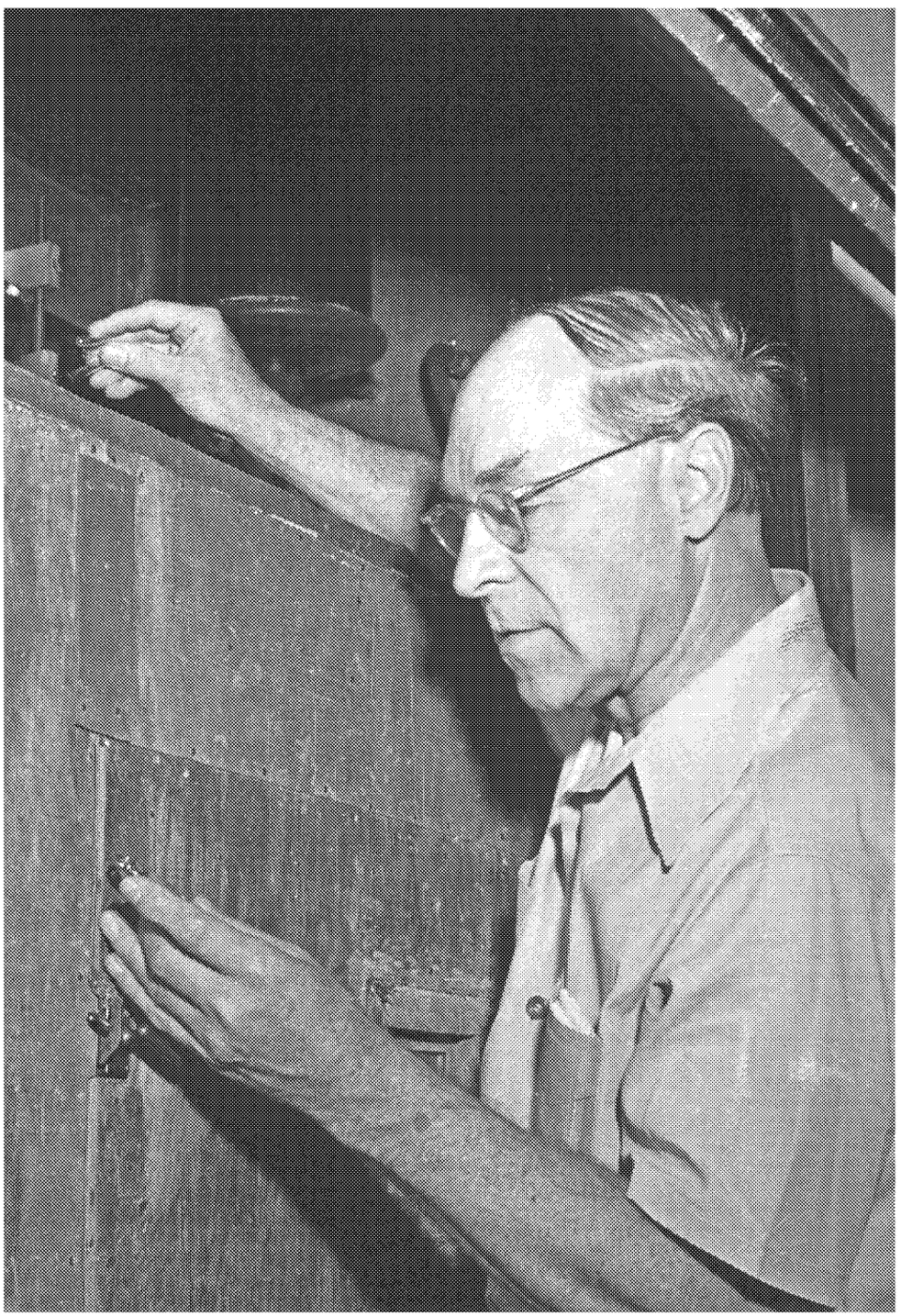
MOUSE EXPERIMENTS SUPPORTING LNT

Muller's gene mutation breakthrough and his formulation of its implications in the Proportionality Law would lead several highly prestigious geneticist and physicist colleagues to provide a mechanism (i.e., gene target theory) of the X-ray-induced gene mutation Proportionality Rule. A 1935 paper presented the "linear non-threshold – single hit model" and applied it to mutation; it would later be applied to cancer. The NAS BEAR Genetics Panel would use this model in its 1956 recommendation.

The model was reaffirmed 16 years later with the next NAS committee, then called the U.S. Biological Effects of Ionizing Radiation (BEIR) Genetics Subcommittee. However, instead of using data from Muller's fruit flies, this committee based the LNT model on the massive mouse model experiments of William Russell of the Oak Ridge National Laboratory. Russell used over 2 million mice in his studies, a size that will likely never be approached again. The findings and the linearity recommendation became the basis for the Environmental Protection Agency's adoption of the LNT model and its regulatory applications to radiation and chemicals. This reflected the belief that cancer was mediated by a commonly shared mutation mechanism.



Hermann Muller preparing one of his genetic experiments exposing fruit flies to X-rays.

The BEIR recommendation has been the "gold standard" for exposure regulation, providing the assurance that linearity was "real" because of the limitations of epidemiological studies to confidently resolve dose-response relationships in the low-dose zone. In many ways, the Russell findings became the toxicology and risk assessment version of the Rosetta Stone. They offered a reliable translation of experimental and epidemiological studies to the language of human risk assessment.

MULLER'S MISTAKE

The above summary is the "official" history of cancer risk assessment offered in most toxicology texts. However, several historical revelations have emerged over the past few years that have turned this entire story upside down. Those revelations affect the reputations of some very prestigious scientists, the validity of a Nobel Prize, and the scientific foundations of cancer risk assessment worldwide.

The problems with the "authoritative" cancer risk assessment story start with its foundation. Muller's claim to have induced gene *mutation* has been found to

be incorrect. He actually induced massive gene *deletions*, affecting chromosome (rather than a gene change) transgenerational phenotypic changes. This criticism of his work was raised while Muller was still alive, but he was able to stifle it. However, modern DNA/nucleotide analysis studies have shown the relevance of this criticism.

Muller's mistakes on the gene mutation interpretation invalidated the 1935 LNT–single hit model that was based on the assumption of gene mutation. Muller mistook an observation (i.e., transgenerational phenotypic changes) for a mechanism (gene mutation), conflating the two. He made a big mistake and perpetuated it for decades, with profound consequences because it infected cancer risk assessment principles and practices.

Fruit flies and a cover-up / The story would grow even more bizarre, involving the atomic bomb–making Manhattan Project of World War II. While the Manhattan Project primarily focused on the bomb, it also had a genetics component designed to assess the effects of ionizing radiation on heredity. That work was conducted at the University of Rochester under the direction of world-renowned geneticist Curt Stern. Muller, then at Amherst College, was a paid consultant.

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The project included a new fruit fly experiment to confirm Stern and Muller's belief in linearity. However, the flies did not co-operate, showing a threshold response in the most extensive study ever conducted on the topic. The findings shocked Stern and his research team, threatening to turn their scientific views and world upside-down.

Stern and co-author Ernst Caspari did write a manuscript presenting the new data, but they directed the scientific community not to accept or use their findings, even though they came from what was clearly the best study yet done on the subject. A reading of preserved letters and memos between the two and other colleagues reveals their fear that the new findings would invalidate the LNT– single hit model. Their work became an effort to "save the hit model" rather than follow the data.

Five weeks before he received his Nobel Prize, Muller received the Stern–Caspari manuscript. He soon wrote Stern acknowledging the great threat the findings posed for the LNT – single hit model and strongly requested the study be repeated. He also admitted that he could find no problem with Caspari as a researcher or with the study.

Despite the new findings, Muller announced at his Nobel lecture that the threshold model should be trashed and replaced with the LNT – single hit model, knowing full well that a better study did not support that claim. Needless to say, he didn't share that information with his Nobel audience. In effect, this started Muller on the road to deliberate deceit and deception, along with Stern, to ensure the acceptance of the LNT – single hit model.

Muller's public deceptions did not stop with his Nobel lecture. He would publish several dishonest and incorrect articles to further the LNT position, all under the watchful eyes of Stern, Caspari, and others. They simply let their Nobel laureate colleague mislead the scientific community and the general public.

PANEL PROBLEMS

The 1956 NAS BEAR I Genetics Panel also exhibited some novel, odd, and troubling features.

First, it was not funded by the U.S. Government, but by the Rockefeller Foundation. Second, the president of the NAS was Detlev Bronk, who also was president of the Rockefeller Institute for Medical Research. In essence, Bronk decided to fund himself. Third, he appointed the chair of the NAS BEAR Genetics Panel, Warren Weaver, who was not a geneticist but a mathematician and who had long worked for the Rockefeller Foundation. Weaver had funded essentially most of the genetic researchers in the United States and elsewhere. Fourth, Weaver and Bronk selected the panel and stacked it with LNT believers, clearly ignoring other geneticists with differing views. Fifth, Weaver selected eight geneticists who had no prior publications on the effects of radiation on mutations. Sixth, during a panel session, Weaver tempted panel members with vast sums of research dollars—a seeming bribe. Seventh, panelist James Crow persuaded his colleagues to alter the research record on two specific matters in order to ensure the likelihood of having the LNT recommendation accepted.

LNT would soon become the law of the land, so to speak, and helped to lead the environmental revolution of the 1960s and 1970s. However, Oak Ridge Labs' Russell reported in December 1958 that the BEAR Panel was wrong when it assumed that all ionizing radiation-induced genetic damage was irreversible and cumulative. He convincingly showed that thresholds could occur at low dose rates, probably because of a DNA repair process. That finding shocked Muller and others. Russell's suggestion on DNA repair was confirmed several years later in research that would earn the 2015 Nobel Prize.

These findings set the stage for the next battle. In 1972, the BEIR Committee acknowledged that the 1956 BEAR Genetics Panel had been wrong and that dose rate, not total dose, was the

key factor for mutation and cancer risk assessment. Russell had shown that at an ionizing radiation exposure rate some 27,000 times above the background exposure, female mice showed a clear threshold—that is, no increase in mutations. While the male mice showed a strong trend in the threshold direction in the same experiment as the females, they had not yet achieved the safe threshold dose. Nonetheless, the BEIR NAS Committee retained the LNT model, relying only on the male mice data.

QUIET REVERSAL

This is where things stood for 25 years, until another Oak Ridge Lab geneticist, Paul Selby (a former student and colleague of Russell), discovered several data problems with the Russell control group. Selby dug into the issue, finding more problems with the research—enough to challenge the key scientific findings. Because of the great sensitivity and significance of these developments, he went to the very top of the Department of Energy and presented his data challenging the Russell findings.

The DOE quietly convened an external panel to evaluate the Selby claims while giving Russell a chance to defend himself. In the end, the panel sided with Selby; Russell had made a major error with his control group data. Russell and Selby both published these revelations in the scientific literature, though they differed on the size of the errors. The corrections were so scholarly written that one could not easily detect the magnitude and significance of the controversy and the underlying hostilities that had emerged. The write-up was amazingly tame and clinical.

These findings sat quietly for another two decades until I came upon them. After obtaining many of the details of the DOE hearing and other information, including a long series of telephone interviews (about 12 hours in total) with Selby, I applied the appropriate correction to the 1972 data used by BEIR to sustain LNT. I found that had the data been corrected at the time of the BEIR I recommendation, it would have supported a threshold rather than the LNT model. Thus, these new findings call into question the "gold standard" that has been guiding U.S. cancer risk assessment since 1977.

CONCLUSION

The story of cancer risk assessment as told by regulatory agencies such as the EPA is really a profound example of flawed science—the product of errors, deception, perverse incentives from academic grants, and ideology. A major remaining question is whether our regulatory agencies can honestly and objectively confront this history and make the needed corrections, or will they simply preserve the historical "lie" that they and society have long been living. If they do the latter, it will continue the harm to both science and public welfare.